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EDITORIAL COMMENT

Matchmaking for the Optimization of Clinical Trials of Heart Failure With Preserved Ejection Fraction

No Laughing Matter*

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Heart failure (HF) with preserved ejection fraction (HFpEF) is common and associated with high morbidity and mortality: HFpEF represents >50% of all HF, and it is growing in prevalence (1); quality of life is generally poor, comparable with that among patients with end-stage renal disease (2); and 5-year survival is only 35% after HF hospitalization (3). In addition, care of patients with HFpEF can be frustrating: the diagnosis is often not straightforward; comorbidities are common and drive outcomes in these patients (4,5); and treatment of patients with HFpEF remains an enigma, with disappointing results from several large randomized controlled trials (6). Thus, it is not surprising that many clinicians feel "therapeutic nihilism" toward HFpEF.

See page 1330

Why have prior clinical trials of HFpEF failed? There are multiple possibilities (7), but for clinicians who care for patients with HFpEF on a frequent basis, it is clear that the heterogeneity of HFpEF is one primary reason (8). HFpEF, like all forms of HF, is a syndrome, not a specific disease process. The overwhelming majority of patients with HFpEF have elevated left ventricular (LV) filling pressures, either at rest or with exertion. However, the severity of the left atrial pressure elevation, volume retention, and consequent pulmonary hypertension with right ventricular dysfunction is variable, as are the etiologic and pathophysiologic paths by which individual patients develop HFpEF. Thus, a "one size fits all" treatment strategy is unlikely to work for patients with HFpEF and may underlie the failures of previous clinical trials.

For future clinical trials of HFpEF to be successful, better matching of therapies with the correct type of HFpEF patient, and endpoints tested, is necessary. Sometimes only in retrospect is it clear that the type of therapy tested in a clinical trial may not be the right match for the types of patients enrolled (or the outcomes tested). Recent examples of this phenomenon include the ALDO-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trial, which enrolled patients with early-stage HFpEF and not overt volume overload (9), and RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction) (10), which enrolled symptomatic patients with volume overload but not necessarily those with overt pulmonary hypertension and right ventricular dysfunction. However, in other studies, the mechanism of the experimental drug is well matched to the type of patients enrolled and the endpoints tested.

In this issue of the *Journal*, Kosmala et al. (11) report their results from just such a study: a short-term, randomized controlled trial of the effects of ivabradine compared with placebo on exercise capacity and hemodynamic status in patients with HFpEF (11). In this small, double-blind clinical trial of 61 patients with early-stage HFpEF and New York Heart Association class II and III symptoms, the investigators randomized study participants to 7 days of ivabradine 5 mg twice daily (n = 30) or placebo (n = 31). All study participants underwent cardiopulmonary exercise testing and diastolic stress echocardiography at baseline and on day 7. The coprimary endpoints were peak oxygen consumption and peak exercise E/e′ ratio (a noninvasive surrogate for LV filling pressure). The results of the trial were impressive: patients randomized to ivabradine had improved exercise capacity, increased peak oxygen consumption, and reduced exercise-induced increases in E/e′. Although the trial was only a short-term 7-day study, the safety and tolerability of ivabradine were also remarkable, with no associated adverse effects and no need for dose reductions or study drug cessation because of bradycardia.

Why was the trial by Kosmala et al. (11) successful? The primary reason may be the drug tested (ivabradine) and its beneficial effects in HFpEF. However, matching the drug and its proposed mechanism of benefit to the right type of HFpEF patient cannot be overemphasized, as shown by analyzing several recent clinical trials of HFpEF (Table 1) (2,9–18). Figure 1 displays a theoretical schema of 3 different HFpEF patient types: exercise-induced diastolic dysfunction (i.e., exercise-induced rise in LV filling pressure), chronic volume overload, and associated right heart failure or pulmonary hypertension. Each type of patient can be classified as having HFpEF; however, the 3 types of HFpEF may represent different stages of the

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Table 1 Summary of Selected Recent or Pending Randomized Controlled Trials of Heart Failure With Preserved Ejection Fraction

First Author/Trial (Ref.#)	Intervention	HFpEF Patient Type*	Primary Endpoint	Trial Result	Trial "Matched" for Rx?
Kosmala et al. (11)	Ivabradine	Exercise-induced DD	Peak Vo_2, peak E/e′ ratio	Positive	Yes
CHAMPION (12)	CardioMEMS sensor	Volume overload	HF hospitalization	Positive	Yes
Guazzi et al. (14)	Sildenafil	Right heart failure/PH	Pulmonary hemodynamic status, RV performance, QoL	Positive	Yes
Kitzman et al. (15)	Exercise training	Exercise-induced DD	Peak Vo_2	Positive	Yes
PARAMOUNT (16)	LCZ696 (ARNI)	Volume overload	ΔNT-proBNP	Positive	Yes
TOPCAT (2)	Spironolactone	Volume overload	CV death, aborted cardiac arrest, or HF hospitalization	Pending	Yes‡
Aldo-DHF (9)	Spironolactone	Exercise-induced DD	Peak Vo_2, ΔE/e′	Negative†	No‡
ELANDD (13)	Nebivolol	Exercise-induced DD	6-min walk test	Negative	No§
J-DHF (17)	Carvedilol (low dose)	Exercise-induced DD/ volume overload	Death or HF hospitalization	Negative	No§
RAAM-PEF (18)	Eplerenone	Volume overload	6-min walk test	Negative	No‡
RELAX (10)	Sildenafil	Volume overload	Peak Vo_2	Negative	No

*HFpEF patient types include exercise-induced DD (ambulatory patients with NYHA class II and III symptoms, grade I DD, and normal or near normal B-type natriuretic peptide levels), chronic volume overload (NYHA class II to IV symptoms with history of HF hospitalization, elevated BNP, and/or left atrial enlargement), and associated right heart failure or PH (NYHA class III and IV symptoms with evidence of pulmonary vascular disease and/or RV dysfunction). See Figure 1 for examples of each patient type. †Aldo-DHF had coprimary endpoints and was negative for the peak Vo_2 endpoint but positive for the ΔE/e′ endpoint. ‡Prior HF trials of mineralocorticoid receptor antagonists have shown that these drugs reduce volume overload and diminish symptoms, but they do not improve exercise capacity or functional class. §Given the vasodilating effects of nebivolol and carvedilol, ELANDD and J-DHF may have been better suited with the chronic volume overload type of patient with HF hospitalization as an endpoint; J-DHF may have been positive had higher doses of carvedilol been used in the study.

Aldo-DHF = Aldosterone Receptor Blockade in Diastolic Heart Failure; ARNI = angiotensin receptor/neprilysin inhibitor; CHAMPION = CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients; CV = cardiovascular; DD = diastolic dysfunction; ELANDD = Effect of Long-Term Administration of Nebivolol on Clinical Symptoms, Exercise Capacity and Left Ventricular Function in Patients With Diastolic Dysfunction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; J-DHF = Japanese Diastolic Heart Failure; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PARAMOUNT = Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction; PH = pulmonary hypertension; QoL = quality of life; RAAM-PEF = Randomized Aldosterone Antagonism in Heart Failure With Preserved Ejection Fraction; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure With Preserved Ejection Fraction; RV = right ventricular; Rx = treatment; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; Vo_2 = oxygen consumption.

HFpEF syndrome or different endophenotypes based on the culmination of environment, diet, comorbidities, and genetic susceptibility.

The trial by Kosmala et al. (11) specifically tested the first type of HFpEF, which is characterized primarily by exercise-induced elevations in LV filling pressures. These patients often do not have significant signs of fluid overload at rest and typically have New York Heart Association functional class II symptoms, normal or near normal natriuretic peptide levels, and grade I diastolic dysfunction on resting echocardiography. Many of these patients do not even require maintenance diuretic therapy. However, with exercise, their LV filling pressures (and left atrial pressures) rise significantly, resulting in exercise intolerance and dyspnea. These patients are not likely to benefit from either spironolactone or phosphodiesterase-5 inhibition, as shown in recent clinical trials (9,10). Instead, a drug with heart rate–lowering and lusitropic effects may be more desirable. Ivabradine is just such as drug.

Ivabradine is a highly selective blocker of inward "funny" channels, which are central regulators of spontaneous depolarization in pacemaker cells (19). Thus, ivabradine selectively decreases heart rate without having negative inotropic or lusitropic effects, as can occur with beta-blockers. Furthermore, animal and human studies have shown that ivabradine can decrease heart rate while improving stroke volume and cardiac output. An elegant study, which used a novel HFpEF animal model, the *db/db* (leptin-receptor deficient) mouse, found that heart rate lowering with ivabradine had several beneficial effects, including reduced effective arterial elastance, increased aortic distensibility, and decreased LV end-systolic elastance (20). In addition, ivabradine accelerated myocardial relaxation by increased phosphorylation of phospholamban, reversing the SERCA2a inhibition that was present in the *db/db* mouse. Improving the activity of SERCA2a has several beneficial downstream effects, including reduction of titin N2B isoform expression and lowering myocardial collagen content (20). Thus, ivabradine may be useful in the short term with its lusitropic and hemodynamic effects, thereby alleviating symptoms and improving exercise capacity, and it may also be useful in the long term, decreasing myocardial stiffness and thereby preventing the development of worsening HF (volume overload).

The study by Kosmala et al. (11) has several strengths, including its use of detailed exercise and echocardiographic testing, specific enrollment criteria (signs and symptoms of HFpEF, evidence of diastolic dysfunction, exercise capacity <80% of age-predicted and sex-predicted values, and E/e′ ratio >13 at peak stress). The 7-day duration of the trial could be viewed as a positive aspect, because it allowed the rapid determination of the drug's efficacy in improving exercise tolerance. Finally, as stated above, perhaps the biggest strength of the study was the accurate "matchmaking" between experimental therapy (ivabradine) and patient type (early-stage HFpEF with primary symptoms of exercise intolerance due to exercise-induced elevations in LV filling pressure).

Several limitations of the study should also be considered. First, the study was small and included only white participants. Thus, the study results may not be generalizable to other HFpEF patient types and populations, and a larger ivabradine trial must be performed in HFpEF before its

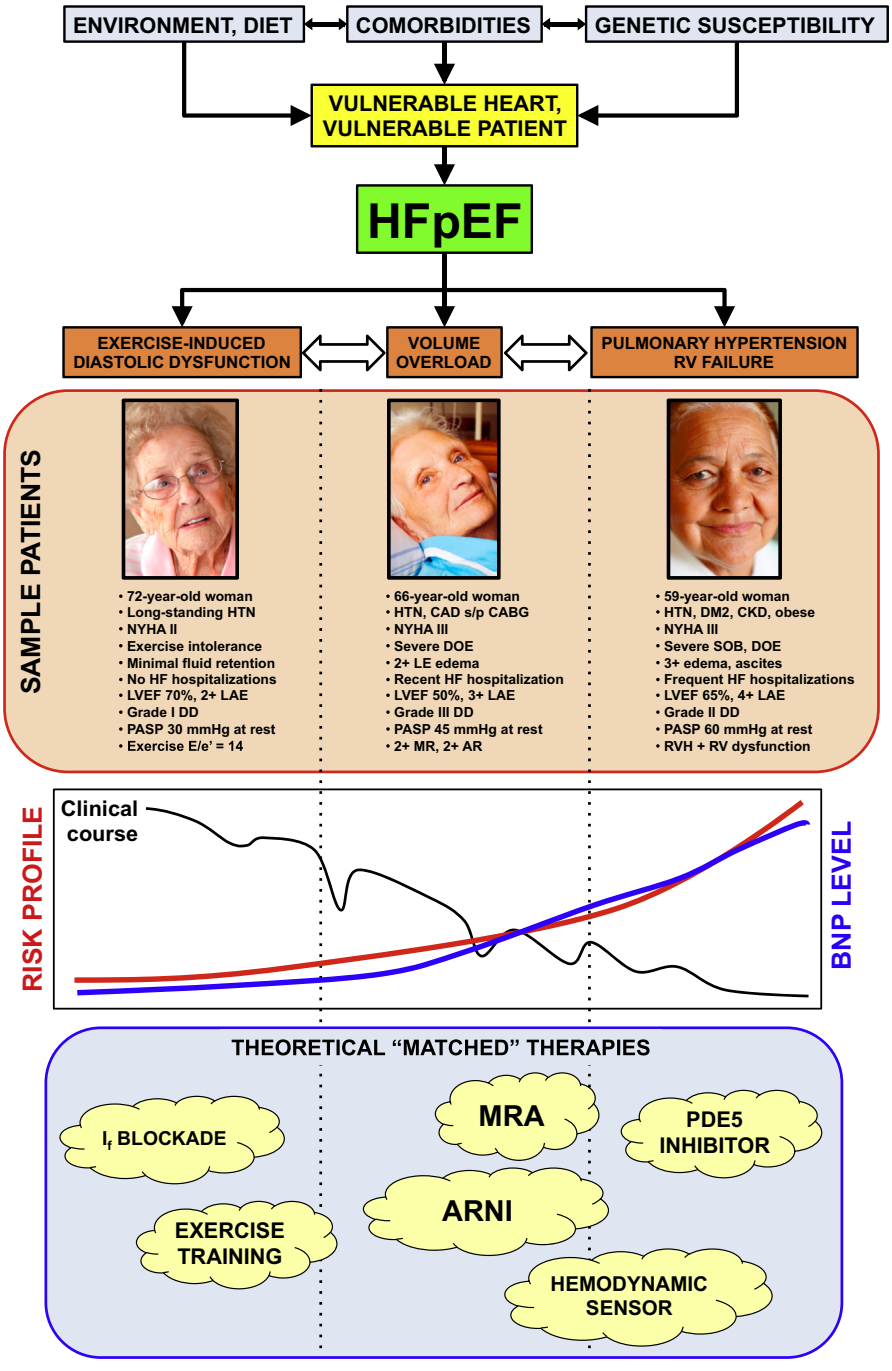

Figure 1 **Theoretical Schema of Heart Failure With Preserved Ejection Fraction Patient Types With Sample Patients, Risk Profiles, and Matched Therapies**

AR = aortic regurgitation; ARNI = angiotensin receptor/neprilysin inhibitor; BNP = B-type natriuretic peptide; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; DD = diastolic dysfunction; DM2 = type 2 diabetes mellitus; DOE = dyspnea on exertion; E/e′ = ratio of early mitral inflow to early mitral annular diastolic tissue velocity; HF = heart failure; HTN = hypertension; I_f = inward "funny" channel; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PDE5 = phosphodiesterase-5; RV = right ventricular; RVH = right ventricular hypertrophy; SOB = shortness of breath; s/p = status post.

use can be advocated in clinical practice. Second, the strict inclusion and exclusion criteria benefited the trial by enrolling only carefully selected patients; however, future larger scale clinical trials of ivabradine in HFpEF must enroll patients using a different strategy than the typical large multicenter HFpEF trials (2), which often use elevated

natriuretic peptides and/or prior HF hospitalization as key inclusion criteria. Third, in HFpEF, heart rate lowering can be problematic in: 1) patients who have advanced diastolic dysfunction and stiff left ventricles (and relatively fixed stroke volumes), because of the dependence on heart rate to augment cardiac output in these cases; and 2) patients who have chronotropic incompetence, in whom heart rate lowering could also exacerbate symptoms (21). Finally, because of the small sample size of the trial, the subgroup analyses presented by Kosmala et al. (11) are limited and thus may have missed adverse effects in problematic patient populations, such as those with lower baseline heart rates or those with undiagnosed chronotropic incompetence.

What are the next steps for ivabradine in patients with HFpEF? On the basis of the data shown in the study by Kosmala et al. (11), a large-scale, longer duration clinical trial of ivabradine should be conducted in patients with HFpEF; however, as noted previously, the inclusion and exclusion criteria should focus on patients with early-stage HFpEF, in whom exercise intolerance is the key symptom and in whom there is objective evidence of exercise-induced increase in LV filling pressure. Elevated natriuretic peptide levels and/or prior HF hospitalization should not be used as entry criteria, because they may result in the selection of patients with more advanced HFpEF, who are unlikely to benefit from ivabradine. Finally, the primary endpoints for a large-scale clinical trial of ivabradine in HFpEF should be exercise capacity and quality of life, with prevention of worsening HF (i.e., HF hospitalization) as a secondary, exploratory endpoint.

In conclusion, Kosmala et al. (11) should be congratulated for carrying out a carefully conducted and detailed exercise hemodynamic study in patients with HFpEF. By taking ivabradine, a blocker of the inward "funny" current, and matching it with the right type of HFpEF patient, coupled with appropriate endpoints (peak oxygen consumption and exercise E/e′ ratio), the investigators were successful matchmakers and may have found a novel therapy for an otherwise difficult-to-manage patient population.

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Key Words: diastolic heart failure ■ heart rate ■ ivabradine ■ randomized controlled trials.